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Note

Synthesis of 2-substituted-1-[(2′-carboxybiphenyl-4-yl) methyl]benzimidazoles

Preet Mohinder Singh Bedi, Raman K Verma*
& Manjeet Singh
Department of Pharmaceutical Sciences and Drug Research,
Punjabi University, Patiala-147 002 (Pb), India.

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A four step synthetic sequence leading to the title compounds through the formation of 4′-methylbiphenyl-2-carboxylic acid via catalysed "Gomberg reaction" is described.

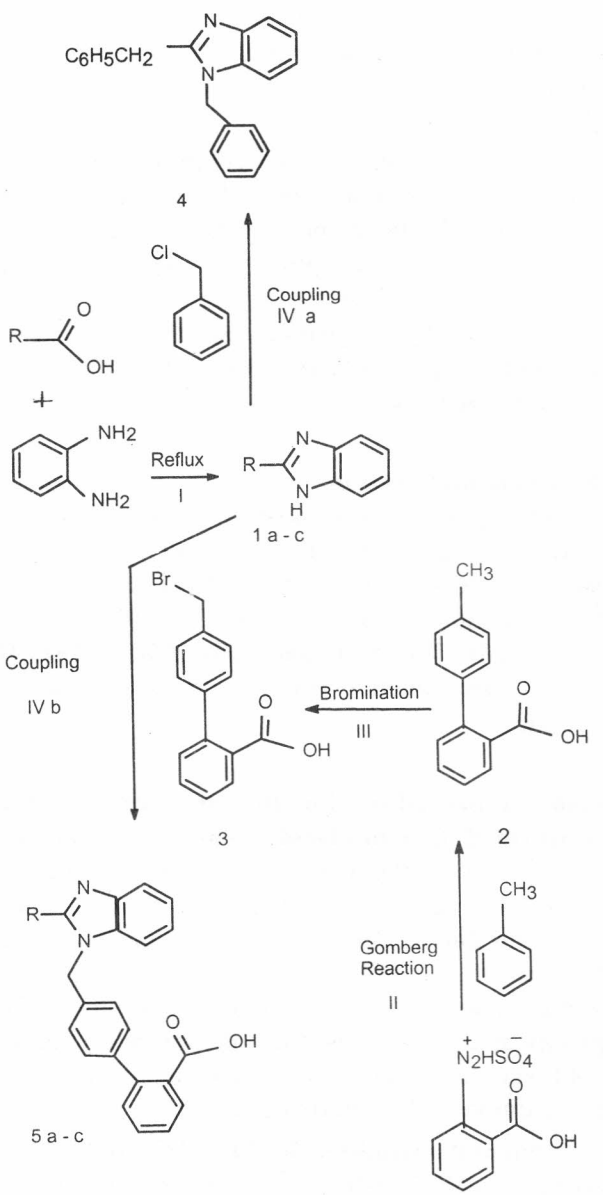
The role of renin-angiotensin system (RAS) to regulate blood pressure and various other cardiovascular functions is well documented[1]. The use of angiotensin II receptor antagonists is perhaps the best possible tool to modulate RAS. Numerous AT_1 selective nonpeptide antagonists have been synthesised in the past several years[2].

Recently efforts have been made to design and synthesise angiotensin II receptor antagonists which can block both AT_1 and AT_2 receptors[3,4]. Such compounds known as 'balanced antagonists' are considered to produce less adverse effects on long term administration. A great number of compounds structurally related to DuP 753[5-8] and its carboxy derivative EXP 7711[2,8] have been synthesised by several laboratories[9,10].

The present note reports a newer synthesis of 2-substituted benzimidazole analogues of EXP 7711, because benzimidazoles are reported to have modest binding affinity for both AT_1 and AT_2 receptors[4,11].

A four step synthetic sequence for the preparation of the title compounds is depicted in Scheme I. The structure of various compounds reported here is confirmed from IR and PMR spectral analysis.

2-Substituted benzimidazoles **1a-c** were prepared from *o*-phenylenediamine and various carboxylic acids under reflux followed by the addition of conc. ammonia solution to precipitate the products.



Scheme I

4′-Methylbiphenyl-2-carboxylic acid[12-14] **2**, m.p. 142°C (lit. m.p. 140°C)[2] was prepared by using the Gomberg reaction[15,16] between the aqueous solution of diazotized anthranilic acid and toluene. Gomberg reaction being slow and poor yielding was later accelerated by the addition of acetonitrile

as co-solvent, which not only catalysed the reaction but also gave improved yields[17].

4′-Methylbiphenyl-2-carboxylic acid **2** is converted into 4′-(bromomethyl) biphenyl-2-carboxylic acid **3** via benzylic bromination with NBS in CCl_4 in the presence of catalytic amount of benzoyl peroxide under reflux. The final step involving the coupling of 2-substituted benzimidazoles[2,5,6] **1a-c** with 4′-(bromomethyl)-biphenyl-2-carboxylic acid **3** was carried out using K_2CO_3 in DMF.

After the success of trial coupling between **1b** and the readily available benzyl chloride giving the expected 1,2-dibenzylbenzimidazole **4**, we then carried out the coupling of **1a-c** with 4′-(bromomethyl)biphenyl-2-carboxylic acid **3** leading to the formation of the desired 2-substituted-1-[(2′-carboxybiphenyl-4-yl) methyl] benzimidazole **5a-c**.

Experimental Section

Melting points were taken in a conc. sulphuric acid bath and are uncorrected (Table-I). IR spectra were recorded in KBr on FTIR-8101, Shimadzu Spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra on AC300F, 300, MHz and BZH 200/52, 200MHz Bruker spectrometers in $CDCl_3$ (chemical shifts in δ, ppm).

General procedure for the preparation of 2-substituted benzimidazoles 1a-c. An equimolar mixture of *o*-phenylenediamine and respective carboxylic acid in 4*N*-HCl were heated under reflux for 2-4 hr. The contents were cooled to room temperature and rendered distinctly alkaline by the gradual addition of conc. ammonia solution. The precipitated solid was filtered, washed with ice cold water and recrystallised from aq. ethanol with the addition of decolourizing carbon.

2-Phenylbenzimidazole 1a. PMR ($CDCl_3$): δ 8.013 (m, 4H), 7.001(m, 5H), 4.661 (br. s, 1H).

2-Benzylbenzimidazole 1b. PMR ($CDCl_3$): δ 7.283 (m, 9H), 4.470 (br.s, 1H), 4.195 (s, 2H, CH_2).

2-Styrylbenzimidazole 1c. IR (KBr): 3400 (NH stretching), 1625 (Aryl conjugated C=C stretching); PMR ($CDCl_3$): δ 7.521 (m, 5H), 7.358 (m, 4H), 7.64, 6.44 (2 doublets, 1H each, CH=CH, J=16Hz), 4.858 (br.s, 1H).

Table I —Physical data of compounds **1-5**

Compd	R	m.p. (°C)	Yield (%)
1a	C_6H_5	291	65
1b	$C_6H_5CH_2$	187	65
1c	C_6H_5CH=CH	120	55
2	—	142	40
3	—	—	80
4	—	192	75
5a	C_6H_5	230	35
5b	$C_6H_5CH_2$	169	35
5c	C_6H_5CH=CH	210	30

4′-Methylbiphenyl-2-carboxylic acid 2. This preparation was carried out using anthranillic acid and involved following two steps:

(a) Diazotization of anthranilic acid. Anthranilic acid (0.01 mole) was added with stirring to 100mL of water containing 14mL of conc. H_2SO_4 and the contents were cooled to 5°C. Diazotized by the gradual addition of (0.101 mole) of sodium nitrite in 20mL of water with continuous stirring to an end point with starch iodide paper.

(b) Gomberg reaction of the diazotized anthranilic acid with toluene. The above diazotized solution was filtered and transferred to a 2L conical flask surrounded by ice water. 400mL of toluene and 40mL of acetonitrile as co-solvent were added to this. The contents were stirred vigorously and to the stirred solution was added an ice cold aq. solution of 80g of sodium acetate trihydrate in 200mL of water in instalments while maintaining the temperature 5-10°C. The stirring continued for 24 hr, after first 3 hr the reaction was allowed to proceed at room temperature. The organic layer was separated, washed with water, dried over anhyd. Na_2SO_4 and excess toluene was removed *in vacuo*. The residue was allowed to cool and treated with dil HCl and more water was added and extracted with ether. The ether extract was washed with water, dried over anhyd. Na_2SO_4 and was concentrated to furnish 40% of **2** as colourless solid m.p. 142°C. IR (KBr): 1700 (C=O stretching of carboxylic acid), 3360-2500 (broad band bonded OH stretching of carboxylic acid), 830 (2 adjacent H), 750 (4 adjacent H); PMR ($CDCl_3$): δ 7.94 and 7.93 (two overlapping doublets, 1H each, *J*=8Hz), 7.530 (t, 2H, *J*=8Hz), 6.968 (m, 4H), 2.375 (s, 3H, CH_3), 10.421 (br. s, 1H, COOH exchangeable).

Preparation of 4′-(bromomethyl)biphenyl-2-carboxylic acid 3. A solution of **2** (0.01 mole), *N*-

bromosuccinimide (0.01 mole) and dibenzoyl peroxide (0.0002 mole) in 150mL of CCl_4 was refluxed for 3 hr. After cooling to room temperature, succinimide was removed by filtration and the filtrate was washed with water, brine and finally with distilled water and dried over anhyd. Na_2SO_4. This upon evaporation afforded 80% of **3** as an yellowish white oil which upon cooling changes to a semi-solid mass. The crude product was used without further purification. PMR ($CDCl_3$): δ 8.127 (d, 2H), 7.935 (m, 1H), 7.914 (m, 1H), 7.542 (m, 2H), 6.949 (m, 2H), 3.040 (s, 2H, CH_2-Br), 10.421 (br. s, 1H, COOH exchangeable).

Coupling of 2-Benzylbenzimidazole (1b) with benzylchloride: (a) Preparation of 1,2-dibenzylbenzimidazole 4. To a suspension of K_2CO_3 (0.03 mole) in 20 mL of DMF at 25°C was added a solution of 2-benzylbenzimidazole **1b** (0.01 mole) in 40 mL of DMF. The resulting solution was stirred for 20 min at 25°C and then a solution of benzylchloride (0.01 mole) in 20 mL DMF was added dropwise and the solution was stirred for 18 hr. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic phase was washed with water, brine and dried over anhyd. Na_2SO_4, filtered and concentrated *in vacuo* to give 75% of **4**, m.p. 192°C. PMR ($CDCl_3$): δ 7.797 (d, 1H) 7.221 (m, 11H), 6.926 (m, 2H), 5.179 (s, 2H, CH_2), 4.248 (s, 2H, CH_2).

Preparation of 2-substituted-1-[(2′-carboxybiphenyl-4-yl)]methyl]benzimidazoles 5a-c. To a suspension of K_2CO_3 (0.015 mole) in 20mL of DMF at 25°C was added a solution of respective 2-substituted benzimidazole (0.005 mole) **1a-c** in 25 mL of DMF. The resulting solution was stirred for 20 min at 25°C and then a solution of **3** (0.005 mole) in 15mL DMF was added dropwise and the solution was stirred for 18 hr. The solvent was removed *in vacuo* and the residue was treated with dil HCl, stirred and partitioned between ethyl acetate and water. The organic phase was washed with water, brine and dried over anhyd. Na_2SO_4, filtered and upon concentration *in vacuo* gave the desired products **5a-c**.

2-Phenyl-1-[(2′-carboxybiphenyl-4-yl)methyl] benzimidazole 5a. PMR ($CDCl_3$): δ 7.952 (m, 6H), 7.530 (m, 2H), 7.002 (m, 9H), 4.210 (S, 2H), 10.90 (br. s, 1H, COOH exchangeable).

2-Benzyl-1- [(2′-carboxybiphenyl-4-yl)methyl]-benzimidazole 5b. PMR ($CDCl_3$): δ 7.4886 (s, 4H), 7.2716 (m, 8H), 7.167 (m, 5H), 4.214, 4.176 (two overlapping singlets 4H (2H each)), 11.75 (br. s, 1H, COOH exchangeable)

2-Styryl-1-[(2′-carboxybiphenyl-4-yl)methyl]-benzimidazole 5c. PMR ($CDCl_3$): δ 7.521 (m, 5H), 7.358 (m, 4H), 7.2716 (m, 8H), 7.64, 6.44 (2 doublets 1H each, CH=CH, *J*=16Hz), 4.210 (s, 2H), 11.10(br. s, 1H, COOH exchangeable).

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